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ORIGINAL ARTICLE

Early initiation of PD therapy in elderly patients is associated with increased risk of death

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ABSTRACT

Background. The effect of early initiation of dialysis on outcomes of patients with end-stage renal disease (ESRD) remains controversial. We conducted this study to investigate the association between the timing of peritoneal dialysis (PD) initiation and mortality in different age groups.

Methods. In this single-centre cohort study, incident patients receiving PD from 1 January 2006 to 31 December 2016 were enrolled. Patients were categorized into three groups according to the estimated glomerular filtration rate (eGFR) at the initiation of PD, with early, mid and late initiation of PD defined as eGFR $\geq$7.5, 5–7.5 and $<$5 mL/min/1.73 m^2, respectively.

Results. A total of 2133 incident patients receiving PD were enrolled with a mean age of 47.1 years, 59.6% male and 25.3% with diabetes, of whom 1803 were young (age $<$65 years) and 330 were elderly (age $\geq$65 years). After multivariable adjustment, the overall and cardiovascular (CV) mortality risks for young patients receiving PD were not significantly different between these three groups. However, for elderly patients, early initiation of PD therapy was associated with increased risks of all-cause {hazard ratio [HR} 1.54 [95% confidence interval (CI) 1.06–2.25]} and CV [HR 2.07 (95% CI 1.24–3.48)] mortality compared with late initiation of PD, while no significant difference was observed in overall or CV mortality between the mid- and late-start groups.

Conclusions. No significant difference in mortality risk was found among the three levels of eGFR at PD therapy initiation in young patients, while early initiation of PD was associated with a higher risk of overall and CV mortality among elderly patients.

Keywords: dialysis initiation, elderly, estimated glomerular filtration rate, mortality, peritoneal dialysis

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INTRODUCTION

End-stage renal disease (ESRD) is now an unquestioned global public health problem and elderly individuals constitute the fastest-growing population of patients with ESRD as a result of rising life expectancies around the world. It is estimated that the number of people receiving renal replacement therapy (RRT) will more than double from 2.618 million in 2010 to 5.439 million worldwide in 2030, with the highest rate of growth in the elderly population [1]. The 2019 US Renal Data System reported that the number of patients on RRT was 743 624 in the USA at the end of 2017, of which elderly patients >65 years of age accounted for 41.5% [2]. In Europe, 564 638 individuals with ESRD were receiving RRT on 31 December 2016, with 42% ≥65 years of age [3]. According to the 2015 Annual Data Report of the China Kidney Disease Network, the estimated numbers of patients receiving hemodialysis (HD) and peritoneal dialysis (PD) were 553 000 and 55 000, respectively, in 2015 in China, with nearly half of patients with chronic kidney disease (CKD) ≥60 years of age [4]. As the burden of ESRD has increased globally, there has been growing recognition of the importance of identifying the optimal time to initiate dialysis, particularly in elderly patients.

Since the 1980s, studies have consistently shown better clinical outcomes in patients who start dialysis 'early' compared with 'late' [5–7], giving rise to a worldwide trend toward earlier initiation of dialysis at higher estimated glomerular filtration rates (eGFRs) over the last few decades. In 2010, the only randomized controlled trial, Initiating Dialysis Early and Late (IDEAL), was published, which demonstrated that there was no significant difference in mortality risk between early and late initiation of dialysis [8]. Since then the trend for earlier initiation of dialysis has been reversed. In the USA, the proportion of incident ESRD patients starting dialysis therapy at an eGFR ≥10 mL/min/1.73 m^2 rose from 12.9% in 1996 to 42.6% in 2010, but decreased to 38.4% in 2017 [2]. A similar trend was found in Canada, where the percentage of patients starting early dialysis therapy (eGFR ≥10.5 mL/min/1.73 m^2) rose from 29% in 2001 to 44% in 2009 [9], while decreasing to 34% in the 2011–15 period [10]. In recent years, some observational studies have indicated that early commencement of dialysis offers no survival benefit or may be harmful [11–16].

As patients receiving PD constitute the minority of patients receiving dialysis, data regarding the relationship between early PD initiation and mortality are scant, especially for elderly patients. Therefore this study investigates the impact of timing of PD therapy initiation on mortality in different age groups.

MATERIALS AND METHODS

Patients and study design

All incident patients who were catheterized in the First Affiliated Hospital of Sun Yat-sen University from 1 January 2006 through 31 December 2016 were enrolled in this retrospective observational cohort study. We excluded patients who were <18 years of age at the initiation of PD, who discontinued PD therapy within 3 months or who transferred from permanent HD or failed renal transplantation.

Data collection and measurements

Prior to PD initiation, last recorded serum creatinine (SCr) values were collected and baseline eGFRs were calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [17]. Incident patients receiving PD were categorized into three groups defined as early, mid and late start according to eGFR ≥7.5, 5–7.5 and <5 mL/min/1.73 m^2, respectively. Demographic and clinical characteristics including age, gender, primary cause of ESRD, body mass index (BMI), history of cardiovascular disease (CVD), presence of diabetes, systolic blood pressure (SBP) and diastolic blood pressure (DBP), baseline biochemical data [including hemoglobin (Hb), serum albumin, uric acid (UA), total cholesterol (Chol), triglycerides (TC), serum albumin–corrected calcium, phosphorus, intact parathyroid hormone (iPTH)] and 24-h urine volume, standard PD test (PET) data and daily ultrafiltration volumes were collected during the first 1–3 months after PD initiation. The presence of CVD was defined as angina, myocardial infarction, congestive heart failure, coronary heart disease, cerebrovascular event or peripheral vascular disease [18]. The comorbidity score was evaluated at baseline according to the Charlson Comorbidity Index (CCI) [19]. Assisted PD was used to describe patients who needed help from others for bag exchange.

Study outcomes and definition

The primary study outcome was all-cause mortality and the second outcome was CV mortality. CV death refers to death due to cardiac arrhythmia, sudden cardiac arrest, acute myocardial infarction, congestive heart failure, cerebrovascular accident or peripheral vascular disease [18, 20]. The causes of death of individuals were reviewed and identified by the PD team in our centre, which consisted of three professional nephrologists. All patients were followed up until death, kidney transplantation, transfer to HD, transfer to other centres or censoring on 31 December 2018.

Statistical analysis

Categorical variables were presented as frequency and percentage, normally distributed continuous variables were expressed as mean with standard deviation (SD) and nonnormally distributed continuous variables were expressed as median with interquartile range (IQR). One-way analysis of variance, Kruskal–Wallis test or chi-squared test were used as appropriate to determine the differences in baseline variables among these three groups.

The Kaplan–Meier method was applied to estimate the survival curves for three groups and differences in the survival distribution were compared using the log-rank test. The association between the timing of PD initiation and all-cause/CV mortality was explored by a Cox proportional hazards regression model and checking the proportional hazards assumptions of the model, calculating the hazard ratio (HR) and 95% confidence interval (95% CI). In the multivariate Cox regression models, we adjusted these covariates with $P < 0.1$ in the univariate regression model or those considered to be risk factors for clinical outcomes, including age, gender, history of CVD, diabetes, SBP, BMI, CCI score, Hb, serum albumin and iPTH. Statistical analysis was performed using SPSS software version 22.0 (IBM, Armonk, NY, USA). A P-value <0.05 was considered to be statistically significant.

Ethical approval

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/index.html) and was approved by the Human Ethics Committees of First Affiliated Hospital, Sun

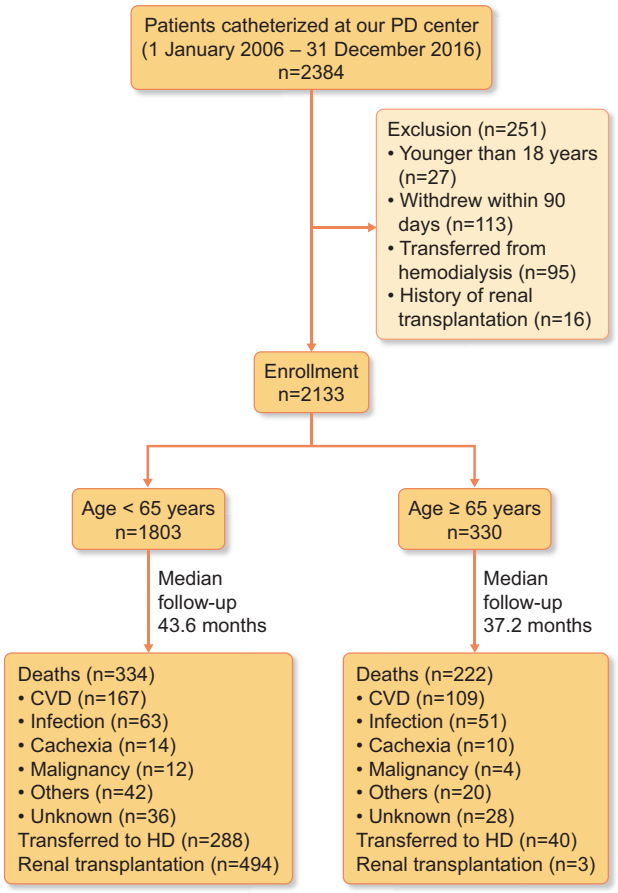

FIGURE 1: Flow chart for study participant enrollment and outcomes.

Yat-sen University. At initiation of PD, all patients were informed that their medical records would be used for noncommercial studies and written informed consent was obtained from all participants.

RESULTS

Study population and baseline characteristics

A total of 2384 incident patients initiated PD treatment in our PD centre from 2006 to 2016, of whom 251 patients were excluded according to the exclusion criteria: 27 were <18 years of age, 113 withdrew within 90 days, 95 were transferred from permanent HD and 16 had a history of renal transplantation. The remaining 2133 patients were enrolled in the analysis, as shown in Figure 1. The young group (age <65 years) consisted of 1803 patients with a mean age of 42.6 years, 61.1% were male, 28.8% had a history of CVD and 19.2% had diabetes. The elderly group (age ≥65 years) consisted of 330 patients with a mean age of 71.2 years, 51.5% were male, 65.5% had a history of CVD and 58.2% had diabetes. The mean eGFRs at the initiation of PD therapy for young and elderly patients were 5.22 and 6.09 mL/min/1.73 m^2, respectively.

Demographic and baseline clinical data of young and elderly individuals according to eGFR at PD initiation are listed in Table 1. There were 244, 597 and 962 young patients and 67, 126 and 137 elderly patients categorized in the early-, mid- and late-start groups, respectively. Among young patients in the study, compared with late initiation of PD, those who started PD earlier were significantly older and were more likely to be male and have a higher comorbidity score, CVD and diabetes, higher serum Hb and higher serum albumin–corrected calcium and lower blood pressure, serum albumin, phosphorus and iPTH. Elderly PD patients in the early-start group were more likely to be male, have a higher CCI score, greater prevalence of diabetes, higher serum albumin–corrected calcium, lower serum albumin and lower iPTH compared with those in the late-start group. Among causes of ESRD, diabetes was more common in the early start group and glomerulonephritis was more common in the late-start group.

Timing of PD initiation and mortality in young patients

During a median 43.6 (IQR 22.3–71.2) months of follow-up, 334 (18.5%) deaths, 288 (16.0%) transfers to permanent HD and 494 (27.4%) kidney transplantations were recorded in the young

Table 1. Baseline characteristics of young (<65 years) and elderly (≥65 years) individuals according to categories of eGFR at initiation of PD

	Age <65 years ($n = 1803$)				Age ≥65 years ($n = 330$)			
Characteristics	Early-start ($n = 244$)	Mid-start ($n = 597$)	Late-start ($n = 962$)	P- value	Early-start ($n = 67$)	Mid-start ($n = 126$)	Late-start ($n = 137$)	P- value
Age (years)	44.4 ± 12.8	42.4 ± 12.3	42.3 ± 11.3	0.037	71.2 ± 4.9	71.5 ± 4.8	71.0 ± 4.9	0.583
Male, *n* (%)	180 (73.8)	412 (69.0)	509 (52.9)	<0.001	46 (68.7)	71 (56.3)	53 (38.7)	<0.001
Primary cause of ESRD, *n* (%)								
Glomerulonephritis	113 (46.3)	380 (63.7)	708 (73.6)	<0.001	10 (14.9)	28 (22.2)	45 (32.8)	0.014
Diabetic nephropathy	95 (38.9)	118 (19.8)	90 (9.4)	<0.001	46 (68.7)	74 (58.7)	46 (33.6)	<0.001
Renal vascular disease	13 (5.3)	42 (7.0)	59 (6.1)	0.613	3 (4.5)	18 (14.3)	26 (19.0)	0.021
Other causes	23 (9.4)	57 (9.5)	105 (10.9)	0.618	8 (11.9)	6 (4.8)	20 (14.6)	0.028
eGFR (mL/min/1.73 m^2)	9.54 ± 2.26	6.02 ± 0.69	3.62 ± 0.87	<0.001	10.67 ± 4.35	6.09 ± 0.72	3.85 ± 0.73	<0.001
BMI (kg/m^2)	21.3 ± 3.0	21.6 ± 3.0	21.7 ± 3.2	0.516	21.9 ± 3.2	22.2 ± 3.2	22.0 ± 3.2	0.722
CCI	3.67 ± 1.61	3.12 ± 1.45	2.78 ± 1.18	<0.001	6.75 ± 1.22	6.48 ± 1.49	5.92 ± 1.49	<0.001
CVD, *n* (%)	90 (36.9)	182 (30.5)	247 (25.7)	0.001	47 (70.1)	87 (69.0)	82 (59.9)	0.195
Diabetes, *n* (%)	101 (41.4)	134 (22.4)	112 (11.6)	<0.001	50 (74.6)	84 (66.7)	58 (42.3)	<0.001
SBP (mmHg)	132.7 ± 19.7	135.9 ± 19.2	137.3 ± 19.5	0.026	132.7 ± 22.4	138.2 ± 21.2	135.4 ± 22.1	0.22
DBP (mmHg)	83.0 ± 13.2	86.3 ± 13.2	88.1 ± 13.1	<0.001	71.3 ± 11.1	73.1 ± 12.0	72.2 ± 10.7	0.642
Hb (g/L)	106.1 ± 21.0	103.9 ± 23.1	98.0 ± 21.5	<0.001	96.6 ± 20.2	94.4 ± 18.4	95.1 ± 21.5	0.812
Serum albumin (g/L)	36.0 ± 5.9	37.2 ± 5.3	37.4 ± 4.9	0.001	33.0 ± 5.3	34.3 ± 4.5	35.3 ± 4.8	0.008
UA (mg/dL)	7.11 ± 1.48	7.26 ± 1.66	7.27 ± 1.60	0.36	6.67 ± 1.62	7.11 ± 1.74	6.98 ± 1.70	0.282
Chol (mmol/L)	5.03 ± 1.36	4.99 ± 1.36	4.99 ± 1.25	0.958	4.90 ± 1.49	4.80 ± 1.16	5.20 ± 1.68	0.204
TC (mmol/L)	1.46 (0.98–2.01)	1.41 (1.01–2.01)	1.35 (0.99–1.91)	0.299	1.62 (1.04–2.09)	1.46 (0.99–2.29)	1.34 (0.99–2.01)	0.572
Calcium[a] (mg/dL)	10.7 ± 1.7	10.4 ± 1.5	10.2 ± 1.4	<0.001	11.6 ± 2.1	11.0 ± 1.6	10.8 ± 1.9	0.011
Phosphorus (mg/dL)	4.23 ± 1.13	4.59 ± 1.38	4.93 ± 1.56	<0.001	4.22 ± 1.24	4.18 ± 1.27	4.51 ± 1.65	0.433
iPTH (pg/mL), median (IQR)	183 (87–308)	228 (119–400)	310 (161–495)	<0.001	129 (68–232)	179 (98–324)	270 (104–433)	0.006
24-h urine volume (mL), median (IQR)	1000 (600–1500)	1000 (650–1600)	1000 (600–1500)	0.004	700 (400–1200)	800 (500–1300)	600 (400–1050)	0.094
PET category, *n* (%)								
High	27 (11.1)	75 (12.6)	122 (12.7)	0.684	11 (16.4)	28 (35.0)	15 (10.9)	0.040
High average	98 (40.2)	232 (38.9)	344 (35.8)	0.608	16 (23.9)	36 (28.6)	40 (29.2)	0.848
Low average	47 (19.3)	107 (17.9)	182 (18.9)	0.302	5 (7.5)	13 (10.3)	23 (16.8)	0.131
Low	3 (1.2)	17 (2.8)	20 (2.1)	0.236	0 (0.00)	3 (2.4)	4 (2.9)	0.457
Daily ultrafiltration volume (mL), median (IQR)	400 (160–620)	400 (100–670)	420 (200–700)	0.626	380 (100–700)	460 (250– 800)	420 (200–650)	0.289
Assisted PD, *n* (%)	92 (37.7)	197 (33.0)	350 (36.4)	0.186	46 (68.7)	77 (61.1)	79 (57.7)	0.260

Variables are presented as mean ± SD unless stated otherwise. Early-start, eGFR ≥7.5 mL/min/1.73 m^2; mid-start, eGFR ≥5–<7.5 mL/min/1.73 m^2; late-start, eGFR <5 mL/min/1.73 m^2.

[a]Calcium, albumin-corrected calcium.

group (age <65 years). Of 334 deaths, 167 (50.0%) were ascribed to CVD, 63 (18.9%) to infection, 14 (4.2%) to cachexia, 12 (3.6%) to malignancy, 42 (12.6%) to other reasons and 36 (10.8%) were classified as reason unknown. For young PD patients at the end of 1, 3 and 5 years, the cumulative patient survival rates were 98, 90 and 77%; 98, 91 and 81%; and 98, 92 and 82%, respectively, in the early, mid- and late-start groups (P = 0.008) (Figure 2A), and the CV mortality rates were 1, 5 and 11%; 1, 5 and 10%; and 1, 5 and 10%, respectively, in these three groups (P = 0.176) (Figure 2B).

As shown in Table 2, in a univariate Cox model using the late-start group as the reference, young patients receiving PD in the early-start group showed a significantly increased risk of all-cause mortality [HR 1.58 (95% CI 1.18–2.11)]; however, HRs were attenuated and lost significance after multivariable adjustment. In the multivariate regression models, compared with young patients in the late-start group, the overall and CV mortality rates were not higher for those in the early- [HR 1.07 (95% CI 0.77–1.50) and HR 0.94 (95% CI 0.57–1.55)] or mid-start [HR 1.00 (95% CI 0.77–1.29) and HR 1.14 (95% CI 0.80–1.62)] groups. The results were similar when we examined eGFR as a continuous variable, which showed no significant association between eGFR level at initiation of PD and overall/CV mortality in young patients.

Timing of PD initiation and mortality in elderly patients

During the median follow-up period of 37.2 (IQR 18.0–53.0) months for elderly (age ≥65 years) patients we observed 222 (67.3%) deaths, 40 (12.1%) transfers to permanent HD and 3 (0.9%) received kidney transplantation. Of 222 patients who died during the observational period, CVD was the primary cause of death [109 (49.1%)], followed by infection [51 (23.0%)], unknown reasons [28 (12.6%)], other reasons [20 (9.0%)], cachexia [10 (4.5%)] and malignancy [4 (1.8%)]. Kaplan–Meier estimates of survival for elderly patients in the early-, mid- and late-start groups are shown in Figure 2C and D. For elderly patients in the early-, mid- and late-start groups, the 1-, 3- and 5-year cumulative patient survival rates were 80, 49 and 28%; 82, 58 and 32%; and 91, 69 and 41%, respectively (P = 0.024), and the CV mortality

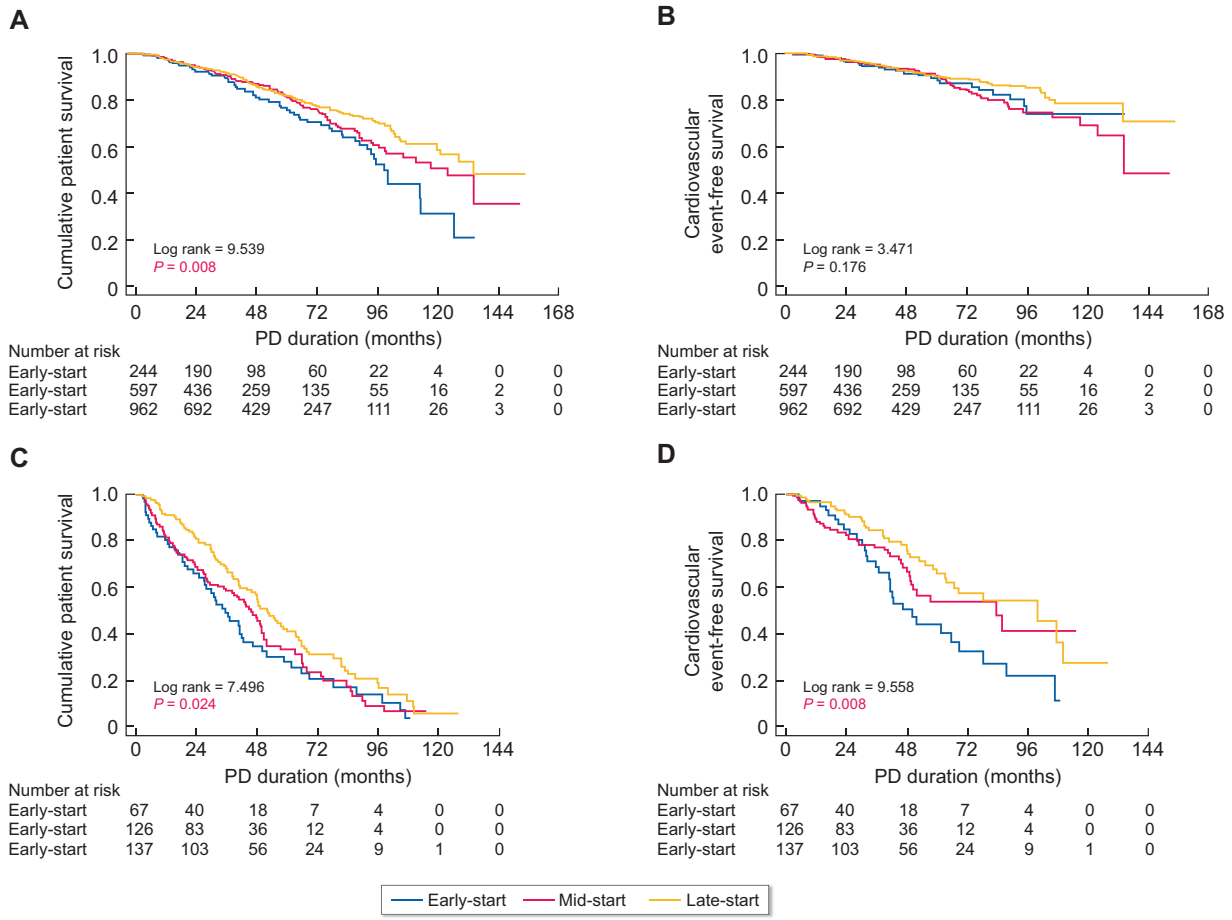

FIGURE 2: Kaplan–Meier analysis of clinical outcomes according to categories of eGFR (mL/min/1.73 m^2) at dialysis initiation (late-start, eGFR <5; mid-start, eGFR ≥5–<7.5; early-start, eGFR ≥7.5): (A) cumulative patient survival, (B) CV event-free survival for young (age <65 years) patients receiving PD, (C) cumulative patient survival and (D) CV event-free survival for elderly (age ≥65 years) patients receiving PD.

Table 2. Association between timing of PD initiation and all-cause and CV mortality in young (age <65 years) patients

eGFR (mL/min/1.73 m^2)	Model 1[a]		Model 2[b]		Model 3[c]		Model 4[d]	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
				All-cause mortality				
Continuous eGFR[e]	1.07 (1.03–1.12)	0.001	1.05 (1.00–1.10)	0.040	1.00 (0.95–1.05)	0.919	1.02 (0.97–1.07)	0.443
≥7.5	1.58 (1.18–2.11)	0.002	1.33 (0.98–1.80)	0.065	0.97 (0.70–1.35)	0.860	1.07 (0.77–1.50)	0.686
5–7.5	1.19 (0.94–1.52)	0.153	1.12 (0.88–1.44)	0.359	0.97 (0.75–1.25)	0.814	1.00 (0.77–1.29)	0.984
<5	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–
				CV mortality				
Continuous eGFR[e]	1.05 (0.99–1.11)	0.144	1.02 (0.95–1.09)	0.586	0.98 (0.91–1.06)	0.627	1.00 (0.93–1.08)	0.923
≥7.5	1.28 (0.81–2.00)	0.289	1.06 (0.67–1.69)	0.794	0.83 (0.51–1.36)	0.463	0.94 (0.57–1.55)	0.797
5–7.5	1.35 (0.97–1.88)	0.074	1.25 (0.89–1.76)	0.195	1.10 (0.78–1.57)	0.580	1.14 (0.80–1.62)	0.458
<5	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–

[a]Unadjusted.
[b]Adjusted for age and gender.
[c]Adjusted for model 1 variables plus history of CVD, diabetes, SBP, BMI and CCI.
[d]Adjusted as in model 3 plus Hb, albumin and iPTH.
[e]Per 1 mL/min/1.73 m^2 higher eGFR.

Table 3. Association between timing of PD initiation and all-cause and CV mortality in elderly (age ≥65 years) patients

eGFR (mL/min/1.73 m^2)	Model 1[a]		Model 2[b]		Model 3[c]		Model 4[d]	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
				All-cause mortality				
Continuous eGFR[e]	1.02 (0.99–1.05)	0.183	1.01 (0.98–1.05)	0.525	1.00 (0.97–1.04)	0.85	1.01 (0.98–1.05)	0.451
≥7.5	1.58 (1.11–2.23)	0.01	1.50 (1.05–2.16)	0.027	1.43 (0.99–2.08)	0.06	1.54 (1.06–2.25)	0.024
5–7.5	1.34 (0.99–1.82)	0.055	1.25 (0.92–1.70)	0.149	1.15 (0.84–1.57)	0.399	1.16 (0.84–1.60)	0.369
<5	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–
				CV mortality				
Continuous eGFR[e]	1.04 (1.00–1.08)	0.06	1.03 (0.98–1.07)	0.256	1.03 (0.98–1.08)	0.246	1.04 (0.99–1.09)	0.138
≥7.5	2.10 (1.30–3.39)	0.002	1.92 (1.17–3.17)	0.01	1.92 (1.15–3.20)	0.012	2.07 (1.24–3.48)	0.006
5–7.5	1.42 (0.91–2.22)	0.119	1.29 (0.82-2.03)	0.265	1.17 (0.73–1.87)	0.509	1.16 (0.72–1.86)	0.538
<5	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–

[a]Unadjusted.
[b]Adjusted for age and gender.
[c]Adjusted for model 1 variables plus history of CVD, diabetes, SBP, BMI and CCI.
[d]Adjusted as in model 3 plus Hb, albumin and iPTH.
[e]Per 1 mL/min/1.73 m^2 higher eGFR.

rates at the end of 1, 3 and 5 years were 3, 31 and 56%; 11, 23 and 47%; and 4, 16 and 34%, respectively (P = 0.008).

The results of the association between timing of PD initiation and mortality in elderly patients from the Cox regression models are summarized in Table 3. Elderly patients showed a significantly increased risk of overall and CV mortality in the early-start group [HR 1.54 (95% CI 1.06–2.25) and HR 2.07 (95% CI 1.24–3.48)] compared with the late-start group, even after multivariable adjustment, while no significant difference was observed in overall or CV mortality between the mid- and late-start groups. A higher eGFR level at initiation of PD therapy was not associated with an increased risk of all-cause or CV mortality in elderly patients when eGFR was examined as a continuous variable.

DISCUSSION

In our observational cohort study, we demonstrated that there was no significant association between the baseline level of eGFR at PD initiation and overall or CV mortality among patients <65 years of age, while early PD initiation (eGFR ≥7.5 mL/min/1.73 m^2) was significantly associated with an increased risk of all-cause and CV mortality among elderly patients (age ≥65 years).

We observed an increase in all-cause mortality associated with a higher eGFR level at PD initiation in young patients; however, the mortality risk of early PD initiation disappeared in a multivariate regression model. Our results are consistent with those of the IDEAL study, which demonstrated that there was no significant difference in overall or CV mortality between early (eGFR 10–14 mL/min/1.73 m^2) and late (eGFR 5–7 mL/min/1.73 m^2) initiation of PD therapy [8, 21]. A cohort study from Canada and a meta-analysis also agree that there is no association between GFR at PD initiation and mortality [9, 22]. Nevertheless, our findings disagree with some of the previous observational studies that suggest early dialysis initiation is associated with increased mortality risk [12–16]. A study of 495 incident patients with PD from Korea found that late commencement of PD (eGFR <5 mL/min/1.73 m^2) was associated with an increased risk of mortality compared with mid-start (eGFR 5–10 mL/min/1.73 m^2), while early initiation of PD (eGFR >10 mL/min/1.73 m^2) showed no survival improvement [23]. Different study design and ethnic variation may account for the discrepancies between their findings and ours.

Our study expands the findings of previous studies by demonstrating that elderly (age ≥65 years) patients initiating PD therapy at higher eGFR levels have increased risk of overall and CV mortality. Elderly patients in the early-start group (eGFR ≥7.5 mL/min/1.73 m^2) experienced a 54% increase in overall mortality and a 107% greater risk of CV death compared with those in the late-start group (eGFR <5 mL/min/1.73 m^2). This result differs from that of Feng *et al.* [24], who enrolled 3286 incident dialysis patients from the Singapore Renal Registry database and demonstrated that early (eGFR ≥10 mL/min/1.73 m^2) versus later (eGFR <5 mL/min/1.73 m^2) commencement of dialysis showed a significantly higher risk of mortality among the nonelderly population (18–64 years) but not among elderly (≥65 years) patients. Another study from Korea showed consistent results, with data from 665 elderly patients (≥65 years) with ESRD, also suggesting that there was no association between the timing of dialysis initiation and clinical outcomes [25]. There are several explanations for the inconsistent results. The modality of RRT was predominantly HD and the proportion of patients receiving PD was relatively small in these studies. Compared with HD, PD has some unique characteristics and different potential risk factors, such as peritonitis, peritoneal protein loss, peritoneal membrane transport status and high glucose load. Furthermore, as residual renal function has been shown be an important determinant of mortality and is better preserved in patients receiving PD than HD [26], the impact of timing of PD initiation on survival may differ from that of HD. Prior studies have demonstrated that the presence of comorbid diseases and lower serum albumin levels are significant risk factors for mortality in elderly patients receiving PD [27, 28]. Previously we reported that older age, diabetes, CVD and malnutrition are associated with both frailty and cognitive impairment among patients on continuous ambulatory PD and that the coexisting frailty and cognitive impairment is related to decreased patient survival rate [29]. In the present study, elderly patients in the early-start group had a higher proportion of diabetes and lower serum albumin compared with the late-start group, which may partly explain the increased mortality of

elderly patients with early dialysis. Another possible explanation for the increased mortality observed in the early-start PD patient group is survivor bias. Specifically, only the fittest patients survived long enough to be included in the late-start group and patients who died before dialysis had started (possibly due to uremia) were excluded. Accordingly, patients in the late-start group showed a spurious survival advantage.

CVD was the primary cause of mortality, accounting for almost 50% of deaths in our study. Our previous study showed a greater prevalence of CVD among elderly patients receiving PD compared with younger patients (53.4% versus 26.0%) [27]. It is well known that the increased risk of CVD in patients receiving PD is due to a combination of traditional, nontraditional and PD-specific risk factors and that interventions targeting some modifiable factors such as hypertension, dyslipidemia, anemia, malnutrition and hyperuricemia may alleviate the risk of CVD and mortality to some extent [30]. Young patients may benefit more from these interventions and no significant difference in survival has been observed between groups. Nevertheless, in our study, patients ≥65 years of age were more likely to present multiple comorbidities than younger patients, thus nonmodifiable factors may be attributed to the excess risk of mortality in patients of advanced age who start PD at a higher eGFR. This reminds us to take a more strategic view of the management of complications to improve the survival of elderly patients receiving PD in the future. Our findings are consistent with current guidelines, which do not recommend preemptive dialysis initiation [31–33]. The 2018 Kidney Disease: Improving Global Outcomes conference suggested that the decision of dialysis initiation may be delayed until eGFR falls to <6 mL/min/1.73 m^2 in older patients (≥60 years) without any absolute clinical indication. The meeting also recommend patient-centered and goal-directed dialysis approaches, providing more individualized care that consolidates patient goals and preferences, while still maintaining best practices for dialysis quality and safety [34]. Taken together, we do not recommend early commencement of PD in the absence of any absolute clinical signs and/or symptoms, and an 'intent-to-defer' strategy may be applicable for elderly patients without compelling indications.

The strengths of our study were the relatively large number of patients receiving PD, comprehensive tracking of outcomes and long-term regular follow-up. What is more, we demonstrated the effect of age on the association between the timing of PD initiation and survival. There were also some limitations to the present study. First, as a single-centre observational study, selection bias via centre-specific effects cannot be excluded. Second, the measurement of SCr was not standardized; although the CKD-EPI equation provides a better estimate of GFR than the Modified Diet in Renal Disease equation, the association between eGFR and mortality is still influenced by muscle mass despite adjustment for BMI and serum albumin. Third, similar to previous observational studies, the results of survival in dialysis patients are subject to several sources of bias, such as lead-time bias and indication bias. Lastly, we could not evaluate the association between early-start patients who initiated PD therapy at eGFR ≥10 mL/min/1.73 m^2 and survival because they constituted a very small proportion of our study population.

CONCLUSIONS

In conclusion, we demonstrated that early-start PD does not contribute significant clinical benefit and is also not detrimental in young patients, while early commencement of PD at an eGFR ≥7.5 mL/min/1.73 m^2 in elderly patients is associated with increased overall and CV mortality. Early initiation of PD based only on the assessment of eGFR without clinical indications cannot be recommended and more strategies aimed at improving survival for patients with advanced age are required.

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AUTHORS' CONTRIBUTIONS

All persons who met authorship criteria are listed as authors and all authors certify that they have participated in the work and take public responsibility for the content, including participation in the design, data collection, analysis, writing or revision of the manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

The authors have no financial conflicts of interest to declare. The results presented in this article have not been published previously in whole or part, except in abstract format.

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